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Docket No.: 40736

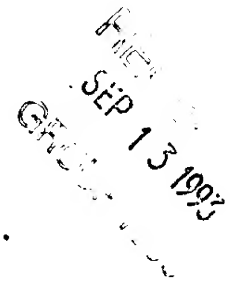
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	D. Panicali	EXAMINER:	D. Barnd
SERIAL NO.:	07/579,269	GROUP:	1813
FILED:	September 5, 1990		

94-2235

FOR: Recombinant Pox Virus For Immunization Against Tumor-Associated Antigens

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231



Sir:

APPEAL BRIEF UNDER 37 CFR 1.192

Applicants respectfully appeal the Final Rejection mailed August 31, 1992, finally rejecting claims 15-22 and 36-37, i.e., all of the claims remaining in the Application.

This brief is being filed in triplicate. A check for the requisite fee for filing this brief, $135.00 is enclosed herewith.

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I. STATUS OF CLAIMS

Claims 1-37 have been presented in the above-identified Application.

Claims 1-14 were withdrawn from consideration pursuant to the Restriction Requirement dated October 1, 1991.

Claims 1-14, 17, and 23-35 were cancelled during prosecution.

Claims 15, 16, 18-22 and 36-37 are presently on appeal (see the attached Appendix).

II. STATUS OF AMENDMENTS (BEFORE AFTER REJECTION)

No Response Under Rule 1.116 was filed by Applicants.

III. SUMMARY OF INVENTION

As set forth at page 3, lines 5-18, the present invention is directed to a method of immunization against a human cellular oncogene encoded product. The method uses recombinant pox virus that expresses the cellular oncogene or proto-oncogene or a homologous oncogene or proto-oncogene to the human cellular oncogene. An oncogene is a gene whose expression results in the malignant transformation of the cell. A proto-oncogene is the gene in its untransformed state and whose expression does not result in malignant transformation. The change of a proto-oncogene to an oncogene can occur by a variety of means including a point mutation resulting in a change of a single critical antigen (e.g. rat *neu, ras*) or increased expression of the proto-oncogene (e.g. human *neu*).

The present process uses a recombinant vector, which is capable of stimulating the immune system and can express an antigen sufficiently related to the human cellular oncogene encoded product to confer protection against that product. The vector and antigen thereby stimulate a broad based immunological response.

IV. ISSUES

(1) Whether claims 15-22, 36 and 37 are patentable under 35 U.S.C. §101 for lack of utility.

(2) Whether claims 15-22, 36 and 37 are patentable under 35 U.S.C. §112, first paragraph, as being non-enabling.

(3) Whether claims 15-22, 36 and 37 are patentable under 35 U.S.C. §112, second paragraph as being indefinite.

(4) Whether claims 15-22 are patentable under 35 U.S.C. §103 over Lathe, et al., Padhy, et al., and further in view of Yamamoto, et al.

V. GROUPING OF CLAIMS

The rejected claims do not stand or fall together since each are considered patentable in their own right.

Applicants believe that all of the claims under appeal are separately patentable for the reasons set forth in the argument section which follows.

VI. ARGUMENT

1. Rejections Under 35 U.S.C. §101

Claims 15-22, 36 and 37 were rejected under 35 U.S.C. §101 for lack of utility.

The present invention is directed to immunizing a human against a tumor, a tumor which is associated with the expression of an oncogene. The present invention is based on the recognition that the normal human immune system does not efficiently deal with human tumor cells in mounting an immunological response thereto. Applicants taught that the vector used for introducing the antigen, for example a virus, particularly a pox virus such as vaccinia, in combination with the antigen could be an effective way of stimulating a broadly based immunological response and that by creating a recombinant vaccinia virus expressing such an antigen, one could get a better immune response than presenting the antigen *per se*.

Applicant's test with mice established that this premise is correct. As shown by Applicants, using a recombinant pox virus, they were able to stimulate the mouse immune system to get a **stronger** immunological response to the tumor. Thus, Applicants proved that the immune system can in fact, regulate or modulate the tumor. Having demonstrated this, Applicants established utility.

In the rat model, a homologous system was used and more precautions are necessary to obtain the desired immune response. Although there were some

problems with the rat model, this does not negate Applicants' showing of utility. Indeed, considerable work on this approach has been continuing in the field.

Utilizing this technology, Applicants are presently involved in human clinical trials. This clinical trial uses a recombinant pox expressing an antigen produced by a tumor, in this instance carcinoembryonic antigen (CEA) which was specified at page 8, line 11 of the present specification. This conclusively establishes the utility of the present invention.

Accordingly, in view of the above, it is believed that the rejection of the claims under 35 U.S.C. §101 should be reversed.

2. Rejections Under 35 U.S.C. §112, first paragraph

The Examiner has objected to the specification and rejected claims 15-22, 36 and 37 under 35 U.S.C. §112, first paragraph, as failing to provide an adequate written description to the invention and failing to adequately teach how to make and use the invention, i.e., failing to provide an enabling disclosure.

As set forth above in response to the rejection under section 101, Applicants' data demonstrates that immunization using a recombinant vaccinia virus containing a heterologous DNA segment encoding a single well-defined antigen, the rat *neu* oncogene can confer protection against mouse tumor cells expressing that antigen. Admittedly, the data also discloses that the vaccinia virus recombinant was not able to result in tumor rejection in a syngeneic system,

namely using the rat *neu* gene product in rats having tumors expressing the rat *neu* gene.

However, Applicants respectfully submit that the present specification enables the skilled artisan to use a recombinant pox virus expressing an oncogene or homologous oncogene against a human cellular oncogene being expressed by a tumor, as set forth in independent claims 15 and 22. As noted above, although the experiments using the same recombinant virus did not work in the rats tested, the skilled artisan would recognize that there are ways to, in essence, prime the immune system to generate an immune response. For example, Applicants did not use the full length *neu*, to eliminate any safety concerns from the use of an oncogenic antigen. However, this meant that the immune system was not presented with the closest antigen available, and an alternative *neu* antigen such as the full length antigen could be used. Alternatively, Applicants did not use the most effective mode of administration to generate an immune response but used an intraperitoneal means. Thus, other modes of administration such as intravenous could readily be used. Alternatively or in combination one could use a method of inoculating, which has a first shot and then a booster shot, screening for a particular adjuvant that enhances the effect or incorporating other immunostimulants such as lymphokines. This is information which the skilled artisan would readily know.

Furthermore, as discussed above, other antigens are continuing to be tested, including work by applicants involving a pox virus capable of expressing CEA, in human clinical trials.

The dependent claims are likewise enabled.

Claim 16 is further patentable because it further specifies that the antigen used is the "oncogene or proto-oncogene product is of human origin."

Claim 18 further recites that the oncogene is "derived from the human oncogene and is rendered inactive with respect to its oncogenic activity by a mutational alteration." Examples of such oncogenes are well know to the skilled artisan and are exemplified at pages of the specification.

The method of Claim 19 further recites that the vector express one of four oncogenes, "neu, ras, trk or kit".

Claims 20 further limits the method of claim 15 to the oncogene of the recombinant pox virus which is a "growth factor receptor molecule." Such oncogenes are well known to the skilled artisan.

Claim 21 further limits the method of claim 20, wherein the specific growth factor receptor is "encoded by the c-erbB gene" is thus further patentable.

Claim 36 is further patentable because it is specifically directed to the method of claim 15, wherein "the oncogene expressed by the recombinant pox virus is derived from a homologous oncogene to the human cellular oncogene."

Claim 37 specifically sets forth that "the homologous oncogene is of rat origin."

Accordingly, in view of the above, it is believed that the rejection of the claims under 35 U.S.C. §112, first paragraph, should be reversed.

3. Rejections under 35 U.S.C. §112, second paragraph

Claims 15-22 and 36-37 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

According to the Office Action the claims are indefinite in their use of the term "cellular oncogene... or a homologous oncogene or proto-oncogene" because it is unclear how such a "homologous" oncogene or proto-oncogene is defined.

Claims are read in light of the specification. *In re Okuzawa*, 190 U.S.P.Q. 550 (CCPA 1970) and in accordance with such understanding to the skilled artisan in the field. These terms have well known meanings and would be perfectly clear to the skilled artisan. For example, the specification, particularly the Examples, show the term "homologous" refers to oncogene or proto-oncogene products having similar structure and function, e.g., the mouse and rat neu gene products.

Accordingly, it is believed that the rejection of the claims under 35 U.S.C. §112, second paragraph is in error and should be reversed.

4. Rejections Under 35 U.S.C. §103

Claims 15-22 were rejected under 35 U.S.C. §103 as being unpatentable over Lathe, et al. in view of Padhy, et al., further in view of Yamamoto, et al.

The present invention is directed to immunizing a human against a tumor, namely a tumor which expresses an oncogene. Applicants have predicted and taught that this method would work.

Claim 15, the only independent claim, relates to "a method of immunizing against a human cellular oncogene encoded product which comprises inoculating an individual having a tumor which expresses the oncogene with a recombinant pox virus which expresses the cellular oncogene or cellular proto-oncogene to the human cellular oncogene, or a homologous oncogene or proto-oncogene to the human cellular oncogene." Claim 19 is substantially restricted to the *neu, ras, trk* or *kit* oncogenes. The remainder of the claims relate to various oncogenes useful in the method of the present invention.

Lathe, et al. in no way discloses or suggests a method for **immunizing against a human cellular oncogene**, nor does the reference suggest use of the specific oncogenes set forth in the claims. Rather, Lathe is directed to a method of immunizing a tumor-bearing animal with a vaccinia virus expressing antigens of polyomavirus. There are considerable differences between the way such a virus operates and the way an oncogene interacts in disease. The antigen Lathe used is highly antigenic as opposed to the antigens of the present invention. Thus, Lathe in no way suggests that the vector used is important in working with the antigen

that is not very effective to stimulate an immune response. Thus, the teaching of Lathe has nothing to do with the present method.

The Examiner has recognized this major difference and attempts to rely on Padhy, et al. and Yamamoto, et al. to fill this gap. However, there is nothing in there two references that teach or suggest that if one was to substitute an oncogene for the polyomavirus antigen of Lathe and use such a recombinant against a tumor expressing the oncogene, one would obtain immunization. Indeed, this is precisely the point the Examiner has made in her rejection of the claims pursuant to 35 U.S.C. §101/§112. These references do not even teach that the immune system would be effective in stopping such tumors. In this case, the prior art offers no suggestion, explicit or implicit that the substitution between the claimed invention in the prior art would provide a reasonable expectation of success. Accordingly, this rejection of the claims should be reversed. See, e.g., *In re Vaeck*, 946 F.2d 488, 493-95 (Fed. Cir. 1991).

It is even clearer that the cited references do not teach, suggest or make obvious the limitations set forth in the dependent claims.

Claim 16 specifically points out that the "oncogene or proto-oncogene product is of human origin." There is no teaching of human use.

Claim 18 recites that the oncogene is "derived from the human oncogene and is rendered inactive with respect to its oncogenic activity by a mutational alteration." This aspect, which is helpful as an added safety measure for the present invention is in no way suggested by the cited references. There is nothing

in these references that teach the added importance of inactivating such antigen.

The method of Claim 19 is directed to the specific oncogenes "*neu, ras, trk* or *kit*." Lathe, et al does not specify the oncogenes encoded by these genes. Nor do the secondary references teach or suggest this combination.

Claims 20 is directed to the method of claim 15 wherein the oncogene of the recombinant pox virus is a "growth factor receptor molecule." This target is not suggested by these references.

Claim 21 is directed to the method of claim 20, wherein the specific growth factor receptor "encoded by the c-erbB gene" is set forth in the claims, and is thus further patentable. This particular target is in no way suggested by the combination.

Claim 36 is specifically directed to the method of claim 15, wherein "the oncogene expressed by the recombinant pox virus is derived from a homologous oncogene to the human cellular oncogene." Claim 37 specifically sets forth "wherein the homologous oncogene is of rat origin." None of the cited references suggest the use of a homologous oncogene, especially one of rat origin.

The above limitations are in no way taught, suggest or made obvious by the cited references, taken alone, or in any reasonable combination.

Accordingly, it is believed that the rejection under 35 U.S.C. §103 should be reversed.

VII. SUMMARY

Therefore, it is respectfully requested that the Board reverse the Examiner in this Application.

Respectfully submitted,

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Date: 9/18/93

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VIII. APPENDIX

15. A method of immunizing against a human cellular oncogene encoded product which comprises inoculating an individual having a tumor which expresses the oncogene with a recombinant pox virus which expresses the cellular oncogene or cellular proto-oncogene to the human cellular oncogene, or a homologous oncogene or proto-oncogene to the human cellular oncogene.

16. The method of Claim 15, wherein the oncogene or proto-oncogene product is of human origin.

18. The method of claim 15, wherein the oncogene of the recombinant pox virus is derived from the human oncogene and is rendered inactive with respect to its oncogenic activity by a mutational alteration.

19. The method of claim 15, wherein the oncogene of the recombinant pox virus is encoded by the neu, ras, trk or kit gene.

20. The method of claim 15, wherein the oncogene of the recombinant pox virus is growth factor receptor molecule.

21. The method of claim 20, wherein the altered receptor molecule is encoded by the c-erbB gene.

22. A method of immunizing an individual against an oncogene or proto-oncogene product encoded by a gene of cellular origin, comprising inoculating the individual afflicted with a tumor bearing the product with an effective amount of a recombinant vaccinia virus which expresses the oncogene or proto-oncogene.

36. The method of claim 15, wherein the oncogene expressed by the recombinant pox virus is derived from a homologous oncogene to the human cellular oncogene.

37. The method of claim 36, wherein the homologous oncogene is of rat origin.